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(54) Title: COMBINATORIAL PROCESS FOR PREPARING TETRAHYDROQUINOLINE LIBRARIES

(57) **Abstract**

This invention relates to a novel diverse combinatorial library of tetrahydroquinoline compounds and to an apparatus providing a readily accessible source of individual members of the library. The apparatus can be used in assay kits and as a replaceable element in automated assay machines.

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# COMBINATORIAL PROCESS FOR PREPARING TETRAHYDROQUINOLINE LIBRARIES

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/032,494, filed December 18, 1996.

## Field of the Invention

The present invention relates to diverse libraries of tetrahydroquinoline compounds, methods of making such libraries, and an apparatus for storing and providing a readily accessible source of diverse tetrahydroquinoline compounds. The apparatus harboring the present combinatorial libraries is a useful component of assay systems for identifying compounds for drug development.

## Background of the Invention

Research and development expenses account for a large outlay of capital in the pharmaceutical industry. Synthesis of compounds is an expensive and time consuming phase of research and development. Historically, research chemists individually synthesized and analyzed high purity compounds for biological screening to develop pharmaceutical leads. Although such methods were successful in bringing new drugs to the market, the limitations of individual synthesis and complete compound characterization considerably slowed the discovery of new pharmaceutically active compounds. The need for more rapid and less expensive drug discovery methodology is increasingly important in today's competitive pharmaceutical industry.

Recently, modern drug discovery has utilized combinatorial chemistry to generate large numbers ($10^2$ - $10^6$) of compounds generically referred to as "libraries". An important objective of combinatory chemistry is to generate a large number of novel compounds that can be

screened to generate lead compounds for pharmaceutical research.

Theoretically the total number of compounds which may be produced for a given library is limited only by the number of reagents available to form substituents on the variable positions on the library's molecular scaffold. The combinatorial process lends itself to automation, both in the generation of compounds and in their biological screening, thereby greatly enhancing the opportunity and efficiency of drug discovery.

Combinatorial chemistry may be performed in a manner where libraries of compounds are generated as mixtures with complete identification of the individual compounds postponed until after positive screening results are obtained. However, a preferred form of combinatorial chemistry is "parallel array synthesis", where individual reaction products are simultaneously synthesized, but are retained in separate vessels. For example, the individual library compounds can be prepared, stored, and assayed in separate wells of a microtiter plate, each well containing one member of the parallel array. The use of standardized microtiter plates or equivalent apparatus, is advantageous because such an apparatus is readily accessed by programmed robotic machinery, both during library synthesis and during library sampling or assaying.

Typically, completion of the solution phase reactions in combinatorial chemistry schemes are ensured by selecting high yielding chemical reactions and/or by using one reagent in considerable excess. When one reagent is used in excess, completion of the reaction produces a mixture of a soluble product with at least one soluble unreacted reagent.

Combinatorial chemistry may be used at two distinct phases of drug development. In the discovery phase diverse libraries are created to find lead compounds. In

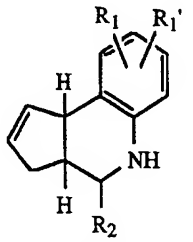
a second optimization phase, strong lead compounds are more narrowly modified to find optimal molecular configurations.

The preparation of selected tetrahydroquinoline compounds by the reaction of cyclopentadiene with imines derived from the condensation of anilines with aldehydes have been described by P.A. Grieco et al., *Tetrahedron Letters*, Vol. 29, pp. 5855-5858 (1988).

The method of the present invention is based on the preparation of a novel diverse library of tetrahydroquinolines useful in the identification of new lead compounds. The library is created, stored, and used as an apparatus comprising of a two-dimensional array of reservoirs, each reservoir containing a predetermined library reaction product differing from those in adjacent reservoirs.

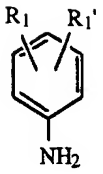
## Summary of the Invention

The present invention provides combinatorial libraries of structurally related compounds having tetrahydroquinoline core structures of the general formula (I):




I

wherein $R_1$ and $R_1$' are substituents derived from an optionally substituted aniline of the formula




and $R_2$ is hydrogen or an organic moiety derived from an aldehyde of the formula $R_2CHO$.

The invention further provides a method for preparing tetrahydroquinoline libraries generally in accordance with Scheme 1 as set forth below.

Another embodiment of the present invention provides an assay kit for the identification of pharmaceutical lead tetrahydroquinoline compounds, said kit comprising assay materials and a well plate apparatus or equivalent apparatus providing a two-dimensional array of defined reservoirs. The well plate apparatus provides a diverse combinatorial library, wherein each well (reservoir) contains a unique reaction product of the tetrahydroquinoline library. The well plate apparatus is used to provide multiple reaction zones for making the library, to store the library and to provide a readily accessible source of library compounds.

## Brief Description of the Drawings

Fig. 1 is a top view of a well plate in accordance with this invention.

Fig. 2 is a side view of a well plate apparatus for use in the process of this invention.

## Detailed Description of the Invention

The term "assay kit" as used in accordance with the present invention refers to an assemblage of two cooperative elements, namely (1) a well plate apparatus and (2) biological assay materials.

"Biological assay materials" are materials necessary to conduct a biological evaluation of the efficacy of any library compound in a screen relevant to a selected disease state.

A "library" is a collection of compounds created by a combinatorial chemical process, said compounds having a common scaffold with one or more variable substituents. The scaffold of the present invention is a tetrahydroquinoline.

A "library compound" is an individual reaction product, a single compound or a mixture of isomers, in a combinatorial library.

A "Lead compound" is a library compound in a selected combinatorial library for which the assay kit has revealed significant activity relevant to a selected disease state.

A "diverse library" means a library where the substituents on the combinatorial library scaffold or core structure, are highly variable in constituent atoms, molecular weight, and structure, and the library, considered in its entirety, is not a collection of closely related homologues or analogues (compare to "directed library").

A "directed library" is a collection of compounds created by a combinatorial chemical process, for the purpose of optimization of the activity of a lead compound, wherein each library compound has a common scaffold, and the library, considered in its entirety, is a collection of closely related homologues or analogues to the lead compound (compare with "diverse library").

The term "scaffold" as used in accordance with the present invention refers to the invariable region (a tetrahydroquinoline core in the present invention) of the compounds which are members of the combinatorial library.

"Substituents" are chemical radicals which are bonded to or incorporated onto the tetrahydroquinoline

scaffold through the combinatorial synthesis process. The different functional groups account for the diversity of the molecules throughout the library and are selected to impart diversity of biological activity to the scaffold in the case of diverse libraries, and optimization of a particular biological activity in the case of directed libraries.

"Reagent" means a reactant, any chemical compound used in the combinatorial synthesis to place substituents on the scaffold of a library.

"Parallel array synthesis" refers to the method of conducting combinatorial chemical synthesis of libraries wherein the individual combinatorial library compounds are separately prepared and stored without prior and subsequent intentional mixing.

"Simultaneous synthesis" means making of library compounds within one production cycle of a combinatorial method (not making all library compounds at the same instant in time).

The "reaction zone" refers to the individual vessel location where the combinatorial chemical library compound preparation process of the invention is carried out and where the individual library compounds are synthesized. Suitable reaction zones are the individual wells of a well plate apparatus.

"Well plate apparatus" refers to the structure capable of holding a plurality of library compounds in dimensionally fixed and defined positions.

"Non-interfering substituents" are those groups that do not significantly impede the process of the invention and yield stable tetrahydroquinoline library compounds.

"Aryl" means one or more aromatic rings, each of 5 or 6 ring carbon atoms and includes substituted aryl having one or more non-interfering substituents. Multiple aryl rings may be fused, as in naphthyl, or unfused, as in biphenyl.

"Alkyl" means straight or branched chain or cyclic hydrocarbon having 1 to 20 carbon atoms.

"Substituted alkyl" is alkyl having one or more non-interfering substituents.

"Halo" means chloro, fluoro, iodo or bromo.

"Heterocycle" or "heterocyclic radical" means one or more rings of 5, 6 or 7 atoms with or without unsaturation or aromatic character, optionally substituted, and at least one ring atom which is not carbon. Preferred heteroatoms include sulfur, oxygen, and nitrogen. Multiple rings may be fused, as in quinoline or benzofuran, or unfused as in 4-phenylpyridine.

"Substituted heterocycle" or "Substituted heterocyclic radical" is heterocycle having one or more non-interfering substituents. Suitable radicals for substitution on the heterocyclic ring structure include, but are not limited to halo, $C_1$-$C_{10}$ alkyl, $C_2$-$C_{10}$ alkenyl, $C_2$-$C_{10}$ alkynyl, $C_1$-$C_{10}$ alkoxy, $C_7$-$C_{12}$ aralkyl, $C_7$-$C_{12}$ alkaryl, $C_1$-$C_{10}$ alkylthio, arylthio, aryloxy, arylamino, $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_{10}$ cycloalkenyl, di($C_1$-$C_{10}$)-alkylamino, $C_2$-$C_{12}$ alkoxyalkyl, $C_1$-$C_6$ alkylsulfinyl, $C_1$-$C_{10}$ alkylsulfonyl, arylsulfonyl, aryl, hydroxy, hydroxy($C_1$-$C_{10}$)alkyl, aryloxy($C_1$-$C_{10}$)alkyl, $C_1$-$C_{10}$ alkoxycarbonyl, aryloxycarbonyl, $C_1$-$C_{10}$ alkanoyloxy, aryloyloxy, substituted alkoxy, fluoroalkyl, nitro, cyano, cyano($C_1$-$C_{10}$)alkyl, $C_1$-$C_{10}$ alkanamido, aryloylamido, arylaminosulfonyl, sulfonamido, heterocyclic radical, nitroalkyl, and -$(CH_2)_m$-Z-($C_1$-$C_{10}$ alkyl), where m is 1 to 8 and Z is oxygen or sulfur.

"Organic moiety" means a substituent comprising a non-interfering substituent covalently bonded through at least one carbon atom. Suitable radicals for substitution onto the connecting carbon atom include, but are not limited to hydrogen, halo, $C_1$-$C_{10}$ alkyl, $C_2$-$C_{10}$ alkenyl, $C_2$-$C_{10}$ alkynyl, $C_1$-$C_{10}$ alkoxy, $C_7$-$C_{12}$ aralkyl,

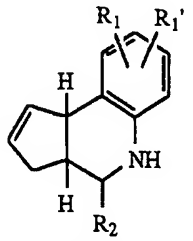
$C_7$-$C_{12}$ alkaryl, $C_1$-$C_{10}$ alkylthio, arylthio, aryloxy, arylamino, $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_{10}$ cycloalkenyl, di($C_1$-$C_{10}$)-alkylamino, $C_2$-$C_{12}$ alkoxyalkyl, $C_1$-$C_6$ alkylsulfinyl, $C_1$-$C_{10}$ alkylsulfonyl, arylsulfonyl, aryl, hydroxy, hydroxy($C_1$-$C_{10}$)alkyl, aryloxy($C_1$-$C_{10}$)alkyl, $C_1$-$C_{10}$ alkoxycarbonyl, aryloxycarbonyl, $C_1$-$C_{10}$ alkanoyloxy, aryloyloxy, substituted alkoxy, fluoroalkyl, nitro, cyano, cyano($C_1$-$C_{10}$)alkyl, $C_1$-$C_{10}$ alkanamido, aryloylamido, arylaminosulfonyl, sulfonamido, heterocyclic radical, nitroalkyl, and -$(CH_2)_m$-Z-($C_1$-$C_{10}$ alkyl), where m is 1 to 8 and Z is oxygen or sulfur.

"Optionally substituted aniline" means aniline or aniline having at least one non-interfering substituent covalently bound to the benzene ring. Suitable radicals for substitution on the benzene ring include, but are not limited to halo, $C_1$-$C_{10}$ alkyl, $C_2$-$C_{10}$ alkenyl, $C_2$-$C_{10}$ alkynyl, $C_1$-$C_{10}$ alkoxy, $C_7$-$C_{12}$ aralkyl, $C_7$-$C_{12}$ alkaryl, $C_1$-$C_{10}$ alkylthio, arylthio, aryloxy, arylamino, $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_{10}$ cycloalkenyl, di($C_1$-$C_{10}$)-alkylamino, $C_2$-$C_{12}$ alkoxyalkyl, $C_1$-$C_6$ alkylsulfinyl, $C_1$-$C_{10}$ alkylsulfonyl, arylsulfonyl, aryl, hydroxy, hydroxy($C_1$-$C_{10}$)alkyl, aryloxy($C_1$-$C_{10}$)alkyl, $C_1$-$C_{10}$ alkoxycarbonyl, aryloxycarbonyl, $C_1$-$C_{10}$ alkanoyloxy, aryloyloxy, substituted alkoxy, fluoroalkyl, nitro, cyano, cyano($C_1$-$C_{10}$)alkyl, $C_1$-$C_{10}$ alkanamido, aryloylamido, arylaminosulfonyl, sulfonamido, heterocyclic radical, nitroalkyl, and -$(CH_2)_m$-Z-($C_1$-$C_{10}$ alkyl), where m is 1 to 8 and Z is oxygen or sulfur.

A diverse library of tetrahydroquinolines is provided in accordance with the present invention. The tetrahydroquinoline library embodied as an apparatus of this invention serves as a readily accessible source of diverse tetrahydroquinoline compounds for use in identifying new biologically active tetrahydroquinoline compounds through pharmaceutical and agricultural candidate screening assays, for use in studies defining

structure/activity relationships, and/or for use in clinical investigation.

The library provided in accordance with the present invention includes tetrahydroquinoline compounds of the formula (I):

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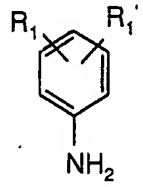
wherein $R_1$ and $R_1'$ are independently hydrogen or non-interfering substituents derived from an optionally substituted aniline of the formula




and $R_2$ is hydrogen or an organic moiety derived from an aldehyde of the formula $R_2CHO$.

In another embodiment of the present invention there is provided a library of compounds of Formula I above, wherein $R_1$ and $R_1'$ are independently selected from the group consisting of hydrogen and non-interfering substituents and $R_2$ is alkyl, substituted alkyl, or aryl.

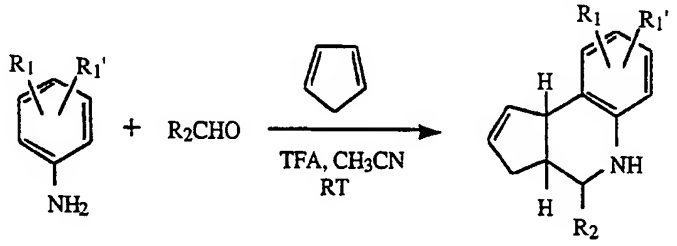
In another embodiment of this invention there is provided a library of compounds of Formula I above, wherein $R_1$ and $R_1'$ are independently selected from hydrogen and non-interfering substituents and $R_2$ is $C_1$-$C_{10}$ alkyl, substituted ($C_1$-$C_{10}$ alkyl), or aryl.

In still another embodiment of the present invention there is provided a library of compounds of Formula I above, wherein $R_1$ and $R_1'$ are independently hydrogen or non-interfering substituents selected from the group

consisting of halo, $C_1$-$C_{10}$ alkyl, $C_2$-$C_{10}$ alkenyl, $C_2$-$C_{10}$ alkynyl, $C_1$-$C_{10}$ alkoxy, $C_7$-$C_{12}$ aralkyl, $C_7$-$C_{12}$ alkaryl, $C_1$-$C_{10}$ alkylthio, arylthio, aryloxy, arylamino, $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_{10}$ cycloalkenyl, di($C_1$-$C_{10}$)-alkylamino, $C_2$-$C_{12}$ alkoxyalkyl, $C_1$-$C_6$ alkylsulfinyl, $C_1$-$C_{10}$ alkylsulfonyl, arylsulfonyl, aryl, hydroxy, hydroxy($C_1$-$C_{10}$)alkyl, aryloxy($C_1$-$C_{10}$)alkyl, $C_1$-$C_{10}$ alkoxycarbonyl, aryloxycarbonyl, $C_1$-$C_{10}$ alkanoyloxy, aryloyloxy, substituted alkoxy, fluoroalkyl, nitro, cyano, cyano($C_1$-$C_{10}$)alkyl, $C_1$-$C_{10}$ alkanamido, aryloylamido, arylaminosulfonyl, sulfonamido, heterocyclic radical, nitroalkyl, or $-(CH_2)_m$-Z-($C_1$-$C_{10}$ alkyl), where m is 1 to 8 and Z is oxygen or sulfur; and $R_2$ is $C_1$-$C_{10}$ alkyl, substituted ($C_1$-$C_{10}$ alkyl).

The present invention also provides a method for preparing the library of tetrahydroquinoline compounds of Formula I using combinatorial chemistry in a parallel array synthesis technique illustrated in the following reaction scheme:

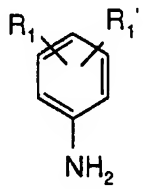
Scheme 1.




The method comprises the steps of reacting series of optionally substituted anilines, optionally substituted aldehydes and cyclopentadiene in the presence of a protic acid, for example trifluoroacetic acid, to prepare a library of tetrahydroquinoline compounds with three sites of diversity, $R_1$ and $R_1$', derived from the aniline reagent, and $R_2$ derived from the aldehyde reagent. Each compound is prepared in a separate reaction zone (i.e.,

parallel array synthesis), and the predetermined product compound is identified by the plate and reaction well number.

The aniline and aldehyde reagents are either commercially available or prepared from commercially available starting materials. Anilines for use in accordance with this invention are compounds of the formula




wherein $R_1$ and $R_1'$ are non-interfering groups, i.e., substituents which do not interfere with the reaction of the the aniline, aldehyde and cyclopentadiene. Typically the aniline reactants have a molecular weight of about 100 to about 600.

Illustrative of suitable anilines for use in preparation of the tetrahydroquinoline library of this invention include, but are not intended to be limited to:

3-Methoxy-5-(trifluoromethyl)aniline
3,5-Bis(trifluoromethyl)aniline
4-Cyclohexylaniline
3-Amino-4-methoxybenzoic acid
5-Aminoisophthalic acid
N1-(4,5-dimethyloxazol-2-yl)sulfanilamide
Sulfathiazole
N1-(6-indazolyl)sulfanilamide
3,4-methylenedioxyaniline

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxylate
N-(4-amino-2-methylphenyl)-4-chlorophthalimide
Sulfadiazine
4-Morpholinoaniline
6-Aminonicotinic acid
6-Aminonicotinamide
3-Aminoquinoline
4-Aminoquinaldine
5-Aminoquinoline
5-Amino-6-nitroquinoline
6-Aminoquinoline
8-Aminoquinoline
3,4-Ethylenedioxyaniline
5-Aminoisoquinoline
2-Bromo-4,6-dinitroaniline
6-Chloro-2,4-dinitroaniline
2,6-Dinitroaniline
2,4,6-Trinitroaniline
2,4-Dinitro-5-fluoroaniline
2,4-Dinitroaniline
4-Methoxy-2-nitroaniline
4-Ethoxy-2-nitroaniline
4-Amino-3-nitrobenzotrifluoride
2,6-Dinitro-4-methylaniline
2-Methoxy-5-nitroaniline
4-Nitroanthranilic acid
3,5-Dinitroaniline
2,5-Dimethoxy-4-nitroaniline
2-Amino-5-nitrobenzonitrile
2-Methoxy-4-nitroaniline
2-Amino-5-nitrobenzophenone
2-Amino-5-nitrobenzotrifluoride
4-Methoxymetanilyl fluoride
4-Amino-1,1'-azobenzene-3,4'-disulfonic acid, sodium salt

4-Aminobenzhydrazide
Aniline
o-Arsanilic acid
2-Aminobenzonitrile
2-Bromoaniline
2,4-Dibromoaniline
2,4,6-Tribromoaniline
2-Bromo-4-methylaniline
2,5-Dibromoaniline
3-Amino-4-bromobenzotrifluoride
2,6-Dibromoaniline
2,6-Dibromo-4-nitroaniline
2,6-Dibromo-4-methylaniline
2-Fluoroaniline
2,3,4,5,6-Pentafluoroaniline
2,3,5,6-Tetrafluoroaniline
4-Amino-2,3,5,6-tetrafluorobenzonitrile
2,4-Difluoroaniline
2,4,5-Trifluoroaniline
2,4,6-Trifluoroaniline
2,5-Difluoroaniline
2-Fluoro-5-nitroaniline
3-Amino-4-fluorobenzotrifluoride
2-Fluoro-5-methylaniline
2,6-Difluoroaniline
2-Chloroaniline
2,3-Dichloroaniline
2,3,5,6-Tetrachloroaniline
4-Bromo-2-chloroaniline
2,4-Dichloroaniline
2,4,5-Trichloroaniline
2,4,6-Trichloroaniline
2,4-Dichloro-6-nitroaniline
2-Chloro-4-nitroaniline
2-Chloro-4-methylaniline
2,5-Dichloroaniline

2-Chloro-5-nitroaniline
3-Amino-4-chloro-n-(2-cyanoethyl)benzenesulfonamide
3-Amino-4-chlorobenzoic acid
2-(3-Amino-4-chlorobenzoyl)benzoic acid
3-Amino-4-chlorobenzotrifluoride
2-Chloro-5-methylaniline
2,6-Dichloroaniline
2,6-Dichloro-3-methylaniline
2,6-Dichloro-4-nitroaniline
2-Chloro-6-methylaniline
2-Amino-3,5-diiodobenzoic acid
2,6-Diiodo-4-nitroaniline
4-Amino-3,5-diiodobenzoic acid
2-Nitroaniline
2-Aminophenol
2-Amino-5-nitrophenol
6-Amino-m-cresol
2-Amino-4-chlorophenol
2-Amino-4-nitrophenol
3-Amino-4-hydroxybenzoic acid
2-Amino-4-tert-butylphenol
2-Amino-p-cresol
3-Hydroxyanthranilic acid
2-Aminobiphenyl
2-Aminothiophenol
Orthanilic acid
2-(Phenylsulfonyl)aniline
2-(2-Chloro-1,1,2-trifluoroethylthio)aniline
2-(Methylmercapto)aniline
Methyl anthranilate
Ethyl 2-aminobenzoate
Anthranilic acid
2-Aminobenzotrifluoride
2-Isopropenylaniline
2-Isopropylaniline
o-Toluidine

p-Toluidine
2-Methyl-3-nitroaniline
2,3-Dimethylaniline
2-Methyl-4-nitroaniline
4-Methoxy-2-methylaniline
4-Amino-3-methylbenzoic acid
2,4-Dimethylaniline
4,6-Dimethyl-2-nitroaniline
2,4,6-Trimethylaniline
2-Methyl-5-nitroaniline
3-Amino-4-methylbenzoic acid
2,5-Dimethylaniline
2-Methyl-6-nitroaniline
2-Amino-3-methylbenzoic acid
2-Isopropyl-6-methylaniline
2,6-Dimethylaniline
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2-Ethylaniline
2-Ethyl-6-methylaniline
2,6-Diethylaniline
2-Aminophenethyl alcohol
3-Aminobenzonitrile
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3-Chloro-4-fluoroaniline
3,4-Dichloroaniline
3,4,5-Trichloroaniline
4,5-Dichloro-2-nitroaniline

3-Chloro-p-anisidine
4-Amino-2-chlorobenzoic acid
3-Chloro-4-methylaniline
3,5-Dichloroaniline
5-Chloro-2-nitroaniline
5-Chloro-o-anisidine
2-Amino-4-chlorobenzoic acid
5-Chloro-2-methylaniline
3-Nitroaniline
m-Anisidine
3-Benzyloxyaniline
m-Phenetidine
3-Aminophenol
3-Amino-o-cresol
Phenyl aminosalicylate
4-Aminosalicylic acid
5-Phenyl-o-anisidine
3-Aminothiophenol
3-(Methylmercapto)aniline
Ethyl 3-aminobenzoate
3-Aminobenzoic acid
3'-Aminoacetophenone
3-Aminobenzotrifluoride
3-(1-Hydroxyethyl)aniline
m-Toluidine
2-Amino-6-methylbenzoic acid
3,4-Dimethylaniline
4,5-Dimethyl-2-nitroaniline
3,5-Dimethylaniline
5-Methyl-2-nitroaniline
2-Methoxy-5-methylaniline
2-Amino-4-methylbenzophenone
3-Aminobenzyl alcohol
3-Ethylaniline
4-Aminobenzonitrile
4-Bromoaniline

2-Amino-5-bromobenzoic acid
4-Bromo-2-methylaniline
4-Bromo-2,6-dimethylaniline
5-Amino-2-bromobenzotrifluoride
4-Bromo-3-methylaniline
4-Fluoroaniline
4-Fluoro-2-nitroaniline
2-Amino-5-fluorobenzotrifluoride
4-Fluoro-2-methylaniline
4-Fluoro-3-nitroaniline
5-Amino-2-fluorobenzotrifluoride
4-Chloroaniline
4-Chloro-2-nitroaniline
Methyl 2-amino-5-chlorobenzoate
2-Amino-5-chlorobenzoic acid
2-Amino-5-chlorobenzophenone
2-Amino-2',5-dichlorobenzophenone
2-Amino-5-chlorobenzotrifluoride
4-Chloro-2-methylaniline
4-Chloro-3-nitroaniline
5-Amino-2-chlorobenzoic acid
5-Amino-2-chlorobenzotrifluoride
4-Chloro-2-methoxy-5-methylaniline
2-Iodoaniline
3-Iodoaniline
4-Iodoaniline
2-Amino-5-iodobenzoic acid
P-Phenylazoaniline
4-Nitroaniline
4'-Amino-n-methylacetanilide
n,n-Dimethyl-p-phenylenediamine
n,n-Diethyl-p-phenylenediamine
4-Phenoxyaniline
p-Anisidine
p-Phenetidine
4-Butoxyaniline

4-Pentyloxyaniline
4-Hexyloxyaniline
4-Aminophenol
2-Amino-5-hydroxybenzoic acid
4-Amino-m-cresol
4-Amino-2,5-dimethylphenol
4-Amino-2,6-dibromophenol
4-Amino-2,6-dichlorophenol
4-Amino-2-nitrophenol
5-Aminosalicylic acid
4-Aminobiphenyl
4-Aminothiophenol
4-Amino-4'-nitrodiphenyl sulfide
4-Aminodibenzenesulfonamide
Sulfanilic acid
4-Hexadecylsulfonylaniline
4-(Methylmercapto)aniline
Methyl 4-aminobenzoate
Ethyl 4-aminobenzoate
4-Aminobenzoic acid
4-Aminobenzophenone
4-Aminoacetophenone
4-Aminobenzotrifluoride hydrochloride
4-Tritylaniline
4-Tert-butylaniline
4-Isopropylaniline
4-Methyl-2-nitroaniline
4-Aminotoluene-3-sulfonic acid
2-Amino-5-methylbenzoic acid
4-Methyl-3-nitroaniline
5-Amino-2-methylbenzenesulfonic acid
4-Aminophenylacetonitrile
Diethyl 4-aminobenzylphosphonate
2,5-Dimethoxy-4'-aminostilbene
4-Aminophenylacetic acid
P-Decylaniline

P-Dodecylaniline
4-Hexadecylaniline
4-Ethylaniline
4-Aminophenethyl alcohol
4-n-Propylaniline
4-n-Butylaniline
4-n-Amylaniline
4-n-Hexylaniline
4-n-Heptylaniline
p-Octylaniline
2-Aminobenzenesulfonamide
4-Amino-6-chloro-1,3-benzenedisulfonamide
Sulfanilamide
2-Aminobenzamide
3-Aminobenzamide
4-Aminobenzamide
4-Amino-2,3,5,6-tetrafluorobenzamide
4-Amino-3,5-dinitrobenzamide
2,5-Dimethoxyaniline
2,4-Dimethoxyaniline
3,5-Dimethoxyaniline
3,4,5-Trimethoxyaniline
3,4-Dimethoxyaniline
Methyl 3,4,5-trimethoxyanthranilate
Dimethyl aminoterephthalate
Dimethyl 5-aminoisophthalate
2,6-Diisopropylaniline
n-(4-Aminobenzoyl)-l-glutamic acid diethyl ester
2-Bromo-4,6-difluoroaniline
Methyl 3-aminothiophene-2-carboxylate
2-n-Propylaniline
p-Tetradecylaniline
n-(4-Aminobenzoyl)-beta-alanine
5-methoxy-2-methyl-4-nitroaniline
2,3-dimethyl-6-nitroaniline
n,n-Dimethyl-4,4'-azodianiline

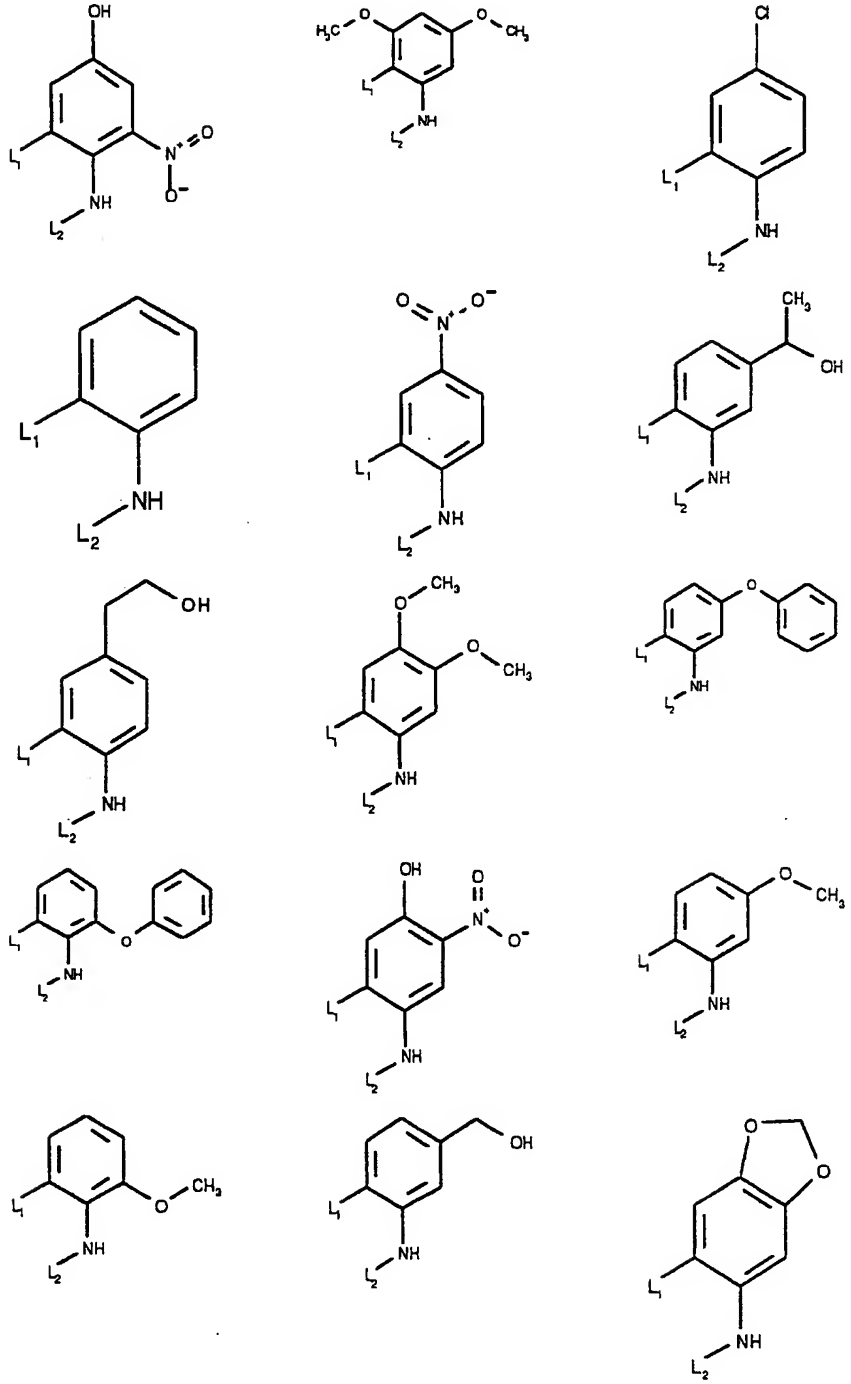
4-Bromo-2-fluoroaniline
5-Amino-2-methoxyphenol
4-Sec-butylaniline
2,3-Difluoroaniline
3-Aminosalicylic acid
2-Amino-4-chloro-5-nitrophenol
2,5-Di-tert-butylaniline
4-Chloro-2-fluoroaniline
4-(4-Nitrophenylsulfonyl)aniline
Methyl 3,5-dibromoanthranilate
Methyl 4-amino-3,5-diiodobenzoate
2-Amino-3-nitrophenol
4,5-Difluoro-2-nitroaniline
2,4,6-Tri-tert-butylaniline
2-Amino-4,5-dimethoxybenzoic acid
2,3,4-Trifluoroaniline
2-Fluoro-4-iodoaniline
4-Amino-n-methylphthalimide
2,4-Dibromo-6-nitroaniline
4-Bromo-2,3,5,6-tetrafluoroaniline
2,3,6-Trifluoroaniline
2-Bromo-3,4,6-trifluoroaniline
2,4,6-Triphenylaniline
4-Aminophenylarsine oxide
5-Amino-2-methylbenzothiazole dihydrochloride
Aniline hydrochloride
o-Toluidine hydrochloride
6-Chloro-m-anisidine hydrochloride
n,n-Dimethyl-m-phenylenediamine dihydrochloride
3-Aminobenzoic acid hydrochloride
3-Aminobenzamidine dihydrochloride
n,n-Dimethyl-p-phenylenediamine monohydrochloride
n,n-Dimethyl-p-phenylenediamine dihydrochloride
n,n-Dimethyl-p-phenylenediamine sulfate
n,n-Diethyl-p-phenylenediamine sulfate
4-Aminoazobenzene hydrochloride

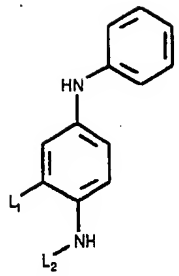
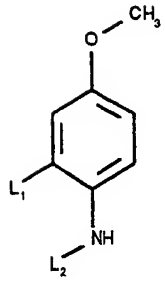
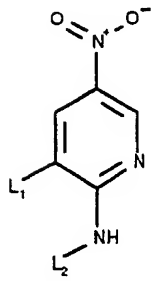
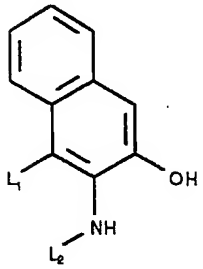
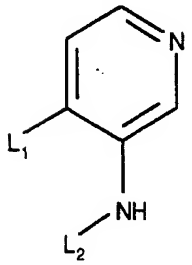
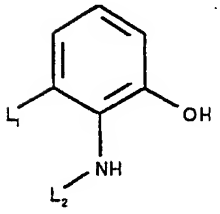
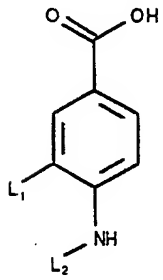
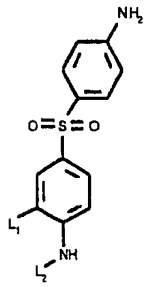
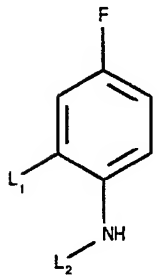
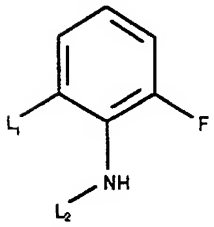
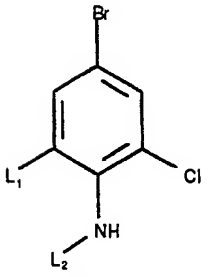
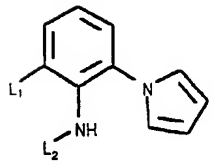
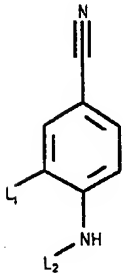
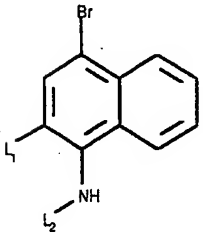
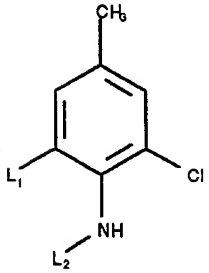
4-Benzyloxyaniline hydrochloride
4-Aminophenol hydrochloride
4-Amino-alpha-diethylamino-o-cresol dihydrochloride
Ethyl 4-aminobenzoate hydrochloride
4-Aminobenzamidine dihydrochloride
Ethyl 3-aminobenzoate, methanesulfonic acid salt
4-Amino-3-nitrobenzonitrile
2-Bromo-4,5,6-trifluoroaniline
4-Bromo-2,6-difluoroaniline
5-Amino-2-nitrobenzotrifluoride
2-Amino-6-fluorobenzonitrile
4-Amino-3-methoxybenzoic acid
2-Amino-4,5-dimethoxyacetophenone
2-Amino-5-nitrobenzoic acid
3,5-Dibromoanthranilic acid
3,5-Dichloroanthranilic acid
4-Amino-3-hydroxybenzoic acid
2-Amino-3,5-dimethylbenzoic acid
Butyl 4-aminobenzoate
2,3,4,5-Tetrafluoroaniline
2-Amino-4-tert-amylphenol
2-Aminotoluene-5-sulfonic acid
1-Butyl-3-sulfanilylurea
5-Tert-butyl-o-anisidine
4-Amino-2,6-diphenylphenol
2-Amino-5-diethylaminotoluene monohydrochloride
6-Amino-2,4-dichloro-3-methylphenol hydrochloride
p-Toluidine hydrochloride
n,n-Diethyl-p-phenylenediamine hydrochloride
2-Phenoxyaniline
4-Amino-2-chlorotoluene-5-sulfonic acid
2-Amino-4-(ethylsulfonyl)phenol
4-Amino-2-chlorobenzonitrile
2-Amino-4-chlorobenzonitrile
4-Amino-5-chloro-2-methoxybenzoic acid
2-Sec-butylaniline

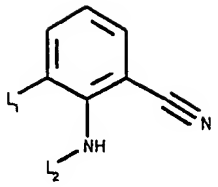
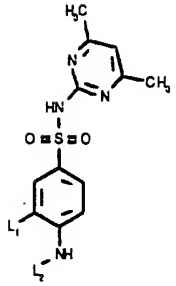
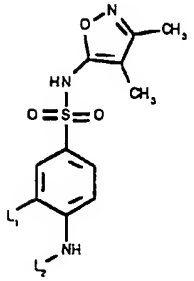
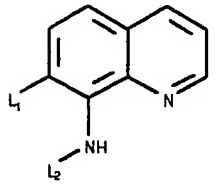
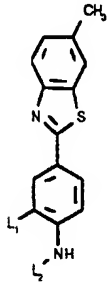
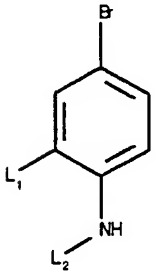
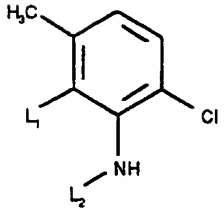
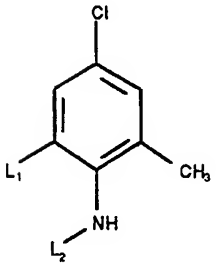
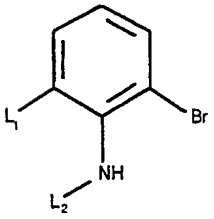
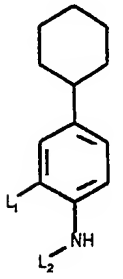
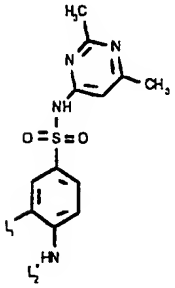
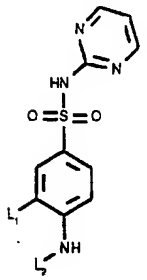
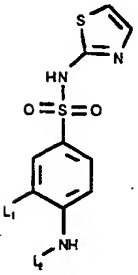
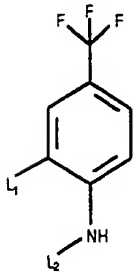
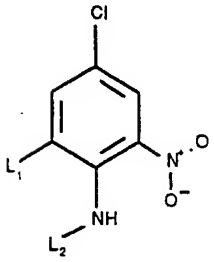
2-Fluoro-4-methylaniline
4-(Trifluoromethoxy)aniline
2,6-Dibromo-4-fluoroaniline
3-(Trifluoromethoxy)aniline
3-Phenoxyaniline
n,n-Dimethyl-p-phenylenediamine oxalate
3-Chloro-2,4-difluoroaniline
2,4-Dibromo-6-fluoroaniline
3-(1,1,2,2-Tetrafluoroethoxy)aniline
2-Bromo-4-fluoroaniline
3-Amino-4-methoxybenzotrifluoride
2-Chloro-4-fluoroaniline
3-Amino-4-mercaptobenzotrifluoride hydrochloride
2,3,4-Trichloroaniline
4-Azidoaniline hydrochloride
3-Chloro-6-methyl-4-nitroaniline
2-Chloro-4,6-dimethylaniline
Aniline-2,3,4,5,6-d5
Menthyl anthranilate
2-Amino-6-chlorobenzoic acid
4-Chloro-2,6-dibromoaniline
2,6-Dichloro-4-(trifluoromethyl) aniline
2-Chloro-4-fluoro-5-methylaniline
2-Amino-5-fluorobenzoic acid
2-Amino-4,5-dimethoxybenzonitrile
2-Amino-4-phenylphenol
3-Amino-2-fluorobenzotrifluoride
2-Amino-3-fluorobenzotrifluoride
2-Amino-5-bromobenzotrifluoride
4-Aminobenzoic acid, sodium salt
and the like anilines.

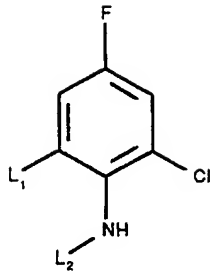
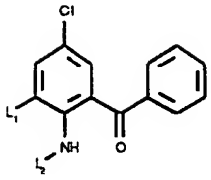
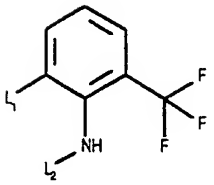
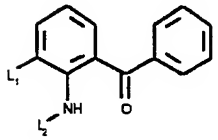
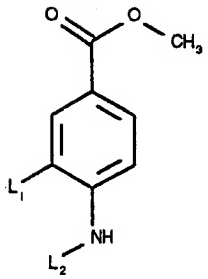
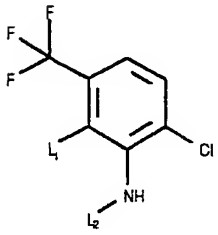
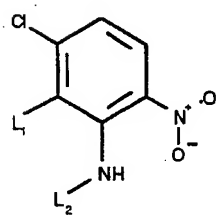
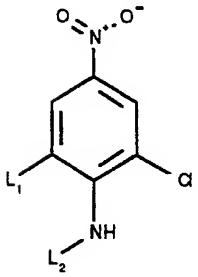
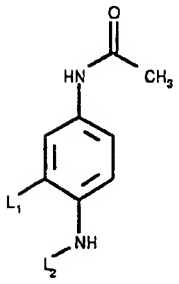
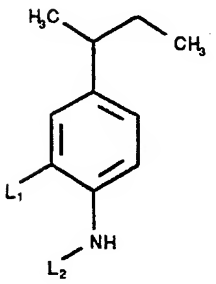
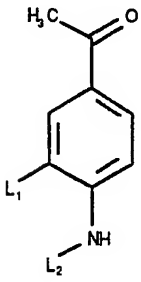
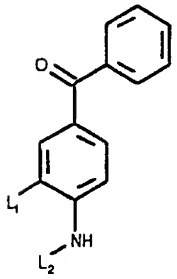
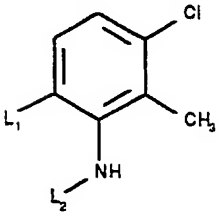
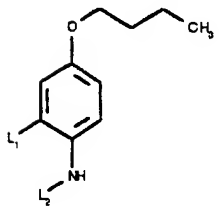
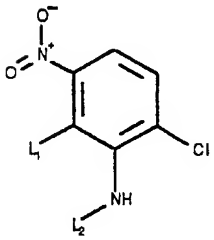
Other suitable anilines for use in preparation of the tetrahydroquinoline library of this invention include, but are not intended to be limited to, those

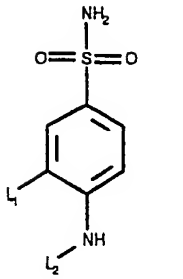
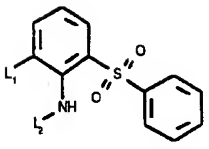
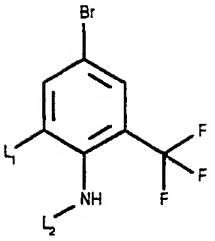
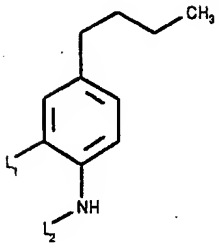
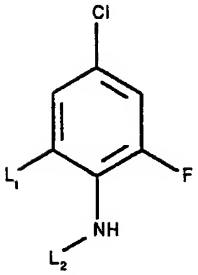
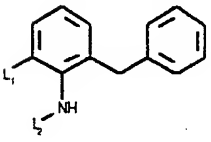
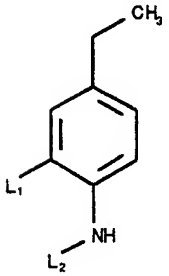
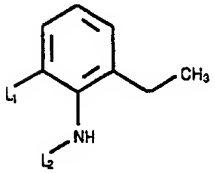
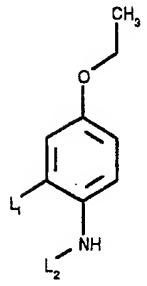
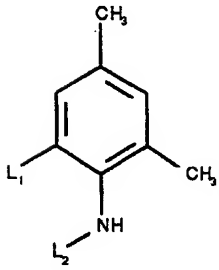
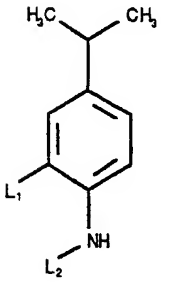
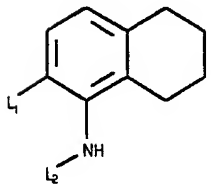
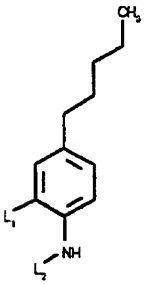
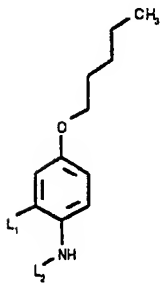
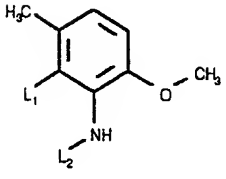
which are illustrated by the following formulas, wherein $L_1$ and $L_2$ are hydrogen:

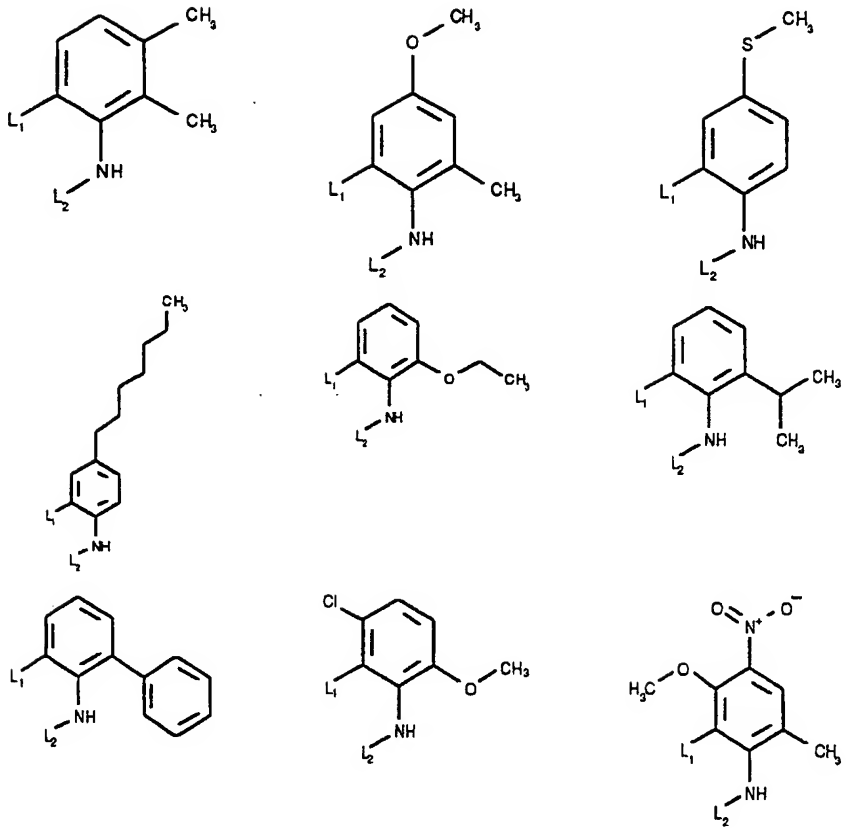




The aldehyde reagents for use in the process for preparing the present library are represented by the general formula $R_2CHO$, wherein $R_2$ is hydrogen or an organic moiety. Typically, aldehyde reagents have a molecular weight ranging from about 50 to about 600.

Illustrative of suitable aldehydes for use in preparation of the tetrahydroquinoline library of this invention include, but are not intended to be limited to:

Cyclohexanecarboxaldehyde
1,2,3,6-Tetrahydrobenzaldehyde
Diphenylacetaldehyde
2-Phenylpropionaldehyde
2,3-Dimethylvaleraldehyde

Isobutyraldehyde
2,6-Dimethyl-5-hepten-1-al
2-Methylbutyraldehyde
2-Ethylbutyraldehyde
2-Methylpentanal
2-Ethylhexanal
2-Methylundecanal
Phenylacetaldehyde
Isovaleraldehyde
7-Methoxy-3,7-dimethyloctanal
Undecanal
Dodecanal
Tridecanal
Tetradecyl aldehyde
Propionaldehyde
3-Phenylpropionaldehyde
3-(Methylthio)propionaldehyde
Butyraldehyde
Cis-4-decen-1-al
N-valeraldehyde
Hexanal
Heptaldehyde
Octanal
Nonanal
Decanal
Undecylenic aldehyde
Cis-11-hexadecenal
Cis-13-octadecenal
Cis-9-hexadecenal
2,5-Dimethoxy-3-tetrahydrofurancarboxaldehyde
3,5,5-Trimethylhexanal
Succinic semialdehyde
(+/-)-3-Phenylbutyraldehyde
2,6,6-Trimethyl-1-cyclohexene-1-acetaldehyde
Cyclopropanecarboxaldehyde
3-Cyclohexylpropionaldehyde

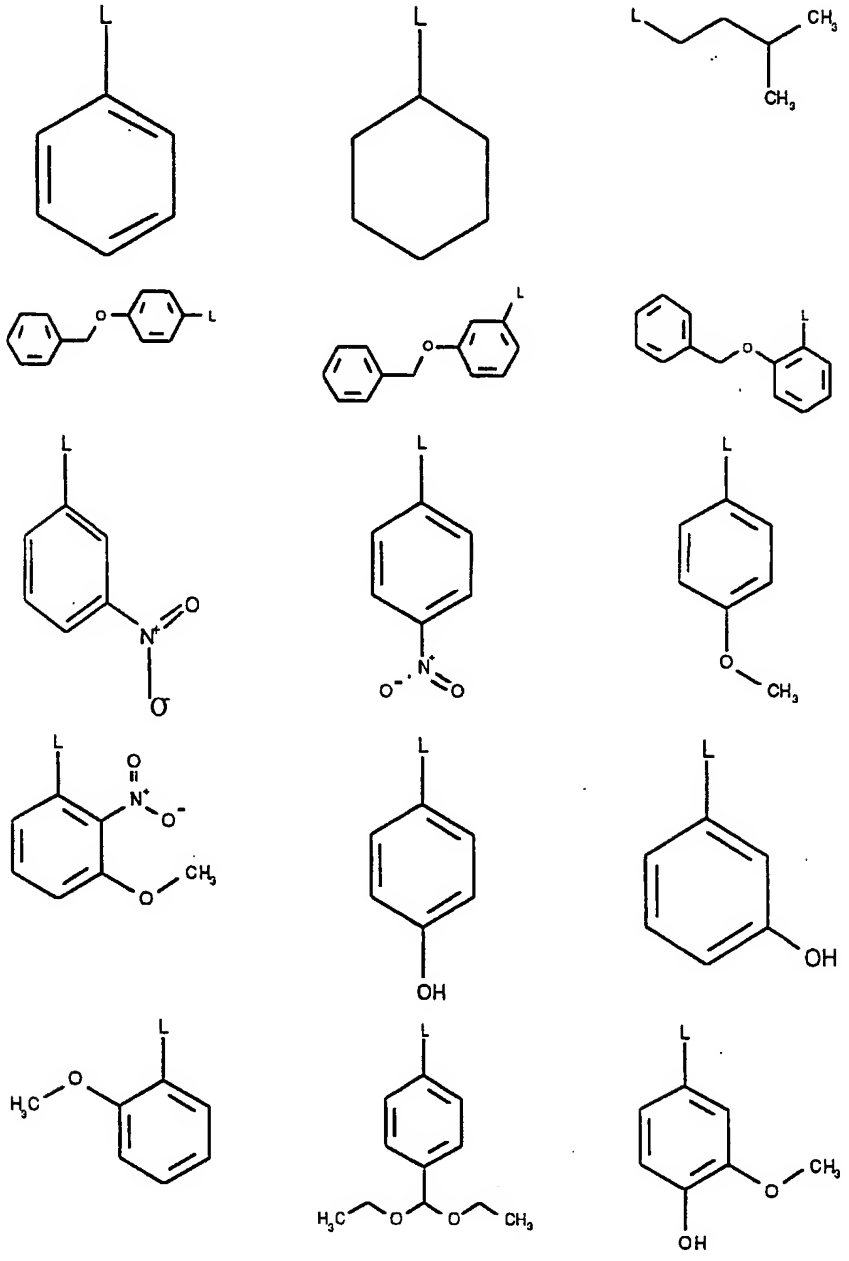
Hydroxycitronellal
Cis-4-heptenal
Cis-6-nonen-1-al
Tetrahydrocitral
Cis-7-decen-1-al
Cis-8-undecen-1-al
3,5,6-Trimethyl-3-cyclohexene-1-carboxaldehyde
Lyral(r)
Bis(2-chlorophenyl)acetaldehyde
2-Thioglyceraldehyde
3-(4-Isopropylphenyl)isobutyraldehyde
2-Ethyl-3-methylbutanal
2-Ethylcaprylaldehyde
3-Methylvaleraldehyde
3-Phenyl-3-(p-tosyl)propionaldehyde
3-Hexenal
3-(Methylthio)butanal
Veltonal
Citronellal
2-(Trifluoromethyl)propionaldehyde
3,3-Dimethylbutyraldehyde
Campholene aldehyde
2-Formylpropionic acid methyl ester
5-Hydroxypentanal
p-Methylphenylacetaldehyde
Omega-ketoheptanoic acid
4-Chlorophenylcyanoacetaldehyde
Hexadecanal
Methyl 7-oxoheptanoate
Diethyl formyl succinate
4-Pregnene-20-beta-carboxaldehyde-3-one
Cis-7-tetradecenal
Cyclopentylmethanal
3,4-Dimethyl-3-cyclohexenylmethanal
2,4,6-Trimethyl-3-cyclohexen-1-carboxaldehyde
Adipic semialdehyde methyl ester

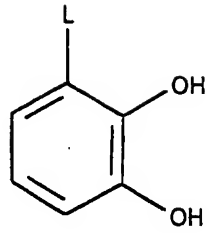
Cis-14-methyl-8-hexadecenal
Cis-3-hexen-1-al
Trans-4-decen-1-al
2,2-Dichlorooctadecanal
2,2-Dichlorotetradecanal
2,2-Dichlorooctanal
2,2-Dichlorohexanal
(r)-(+)-Citronellal
8-Methyl-7-nonenal
2-(p-Tolyl)propionaldehyde
Aldehyde C-11 MOA (2-methyldecanal)
Alpha-methylhydrocinnamaldehyde
(s)-(-)-Citronellal
4-Hydroxybutanal
4-Oxobutyric acid methyl ester
3,3,4,4,5,5,5-Heptafluoropentanal
3-Methylbutanal-1-13c
6-Methyl-3-cyclohexene-1-carboxaldehyde
4-(4-Methyl-2-pentenyl)-3-cyclohexene-1-carboxaldehyde
3-Pentyn-1-al
3-Pyridylacetaldehyde n-oxide
2,3-Dihydro-5-methoxy-3-phenyl-2-indolecarboxaldehyde
2,4-Diphenyl-3-oxobutyraldehyde
3,3,3-Triphenylpropionaldehyde
2-Bromo-n-(3-formyl-1-methylpropyl)benzamide
3-(Phenylthio)butyraldehyde
Diethyl 2-(diethoxymethyl)-3-formylsuccinate
2-Chloro-3-(4-nitrophenyl)-propionaldehyde
2-Acetoxypropionaldehyde
2-Methyl-4-phenylpentanal
(1r,2s,3r,4s)-(+)-2-Benzyloxy-3-formyl-oxybornane
5-(4'-Chlorophenoxy)-1-pentanal
Boc-ala-CHO
Boc-leu-CHO

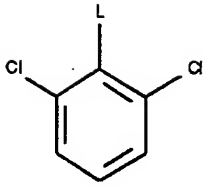
Boc-phe-CHO
Boc-tyr(OBzl)-CHO
Boc-tyr(OMe)-CHO
Boc-val-CHO
4-Pentenal
1-Formyl-6-(dimethylamino)fulvene
1,4-Dioxaspiro(4.5)decane-7-acetaldehyde
Alpha-citronellal
Diethyl 2-Acetamido-2-(2-formylethyl)malonate
3,4,4,5,5,5-Hexafluoro-3-(trifluoromethyl)pentanal
3,4,4,4-Tetrafluoro-3-(heptafluoropropoxy)butanal
3,4,4,4-Tetrafluoro-3-(trifluoromethoxy)butanal
3,4,4,4-Tetrafluoro-3-(trifluoromethyl)butanal
3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctanal
3,3,3-Trifluoropropanal
Beta,beta-dimethylhydrocinnamaldehyde
5-Norbornene-2-carboxaldehyde
Chrysanthal
9-Decenal
Decyl aldehyde, [1-14c]
4,4,4-Trifluorobutyraldehyde
3-Methyl-3-butenal
3-(5-Methyl-2-furyl)butanal
3-Phenyl-4-pentenal
Tert-butyl (s)-4-formyl-2,2-dimethyl-3-
oxazolidinecarboxylate
Trans-2-dodecenal
9,10-Dihydro-9,10-ethanoanthracene-11-carboxaldehyde
Methyl hexyl acetaldehyde
2,3-Dihydro-2-oxo-1H-imidazol-4-carboxaldehyde
N-Acetylmuramic acid,
and the like aldehydes.

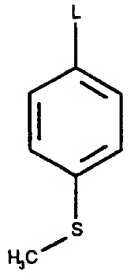
Particularly suitable aldehydes useful for forming the imine intermediates in preparation of the present

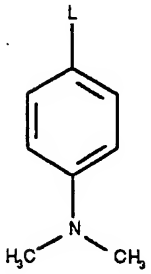
tetrahydroquinoline libraries are further illustrated by the following formulas, wherein L is -CHO:

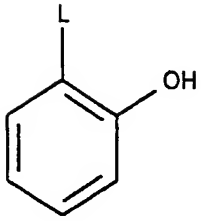


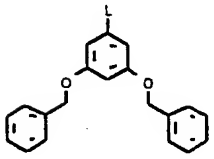

L
OH
OH

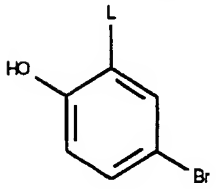

L
Cl
Cl

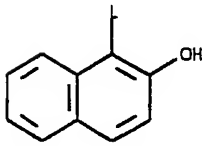

L
S
H3C

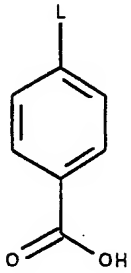

L
N
H3C
CH3

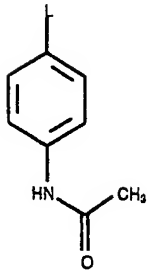

L
OH

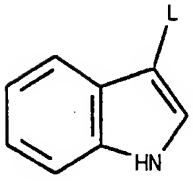

L
O
O

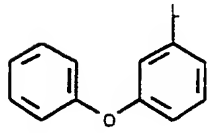

L
HO
Br

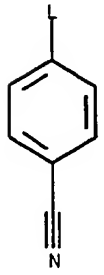

L
OH

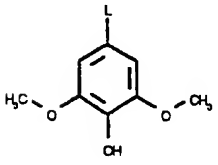

L
O
OH

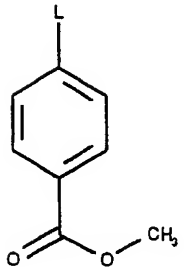

L
HN
CH3
O

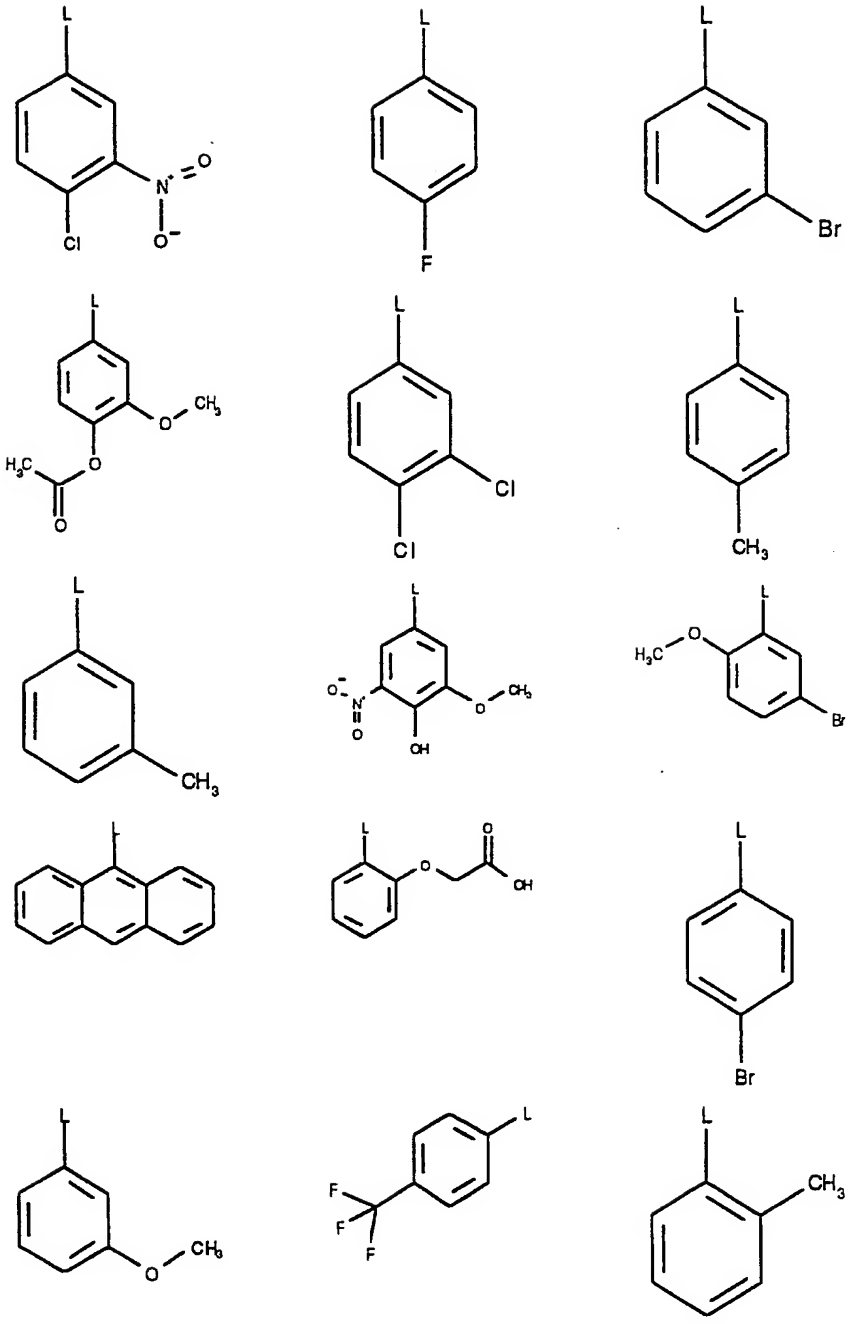

L
HN


L
O


L
N


L
H3C
O
O
CH3
OH


L
O
O
CH3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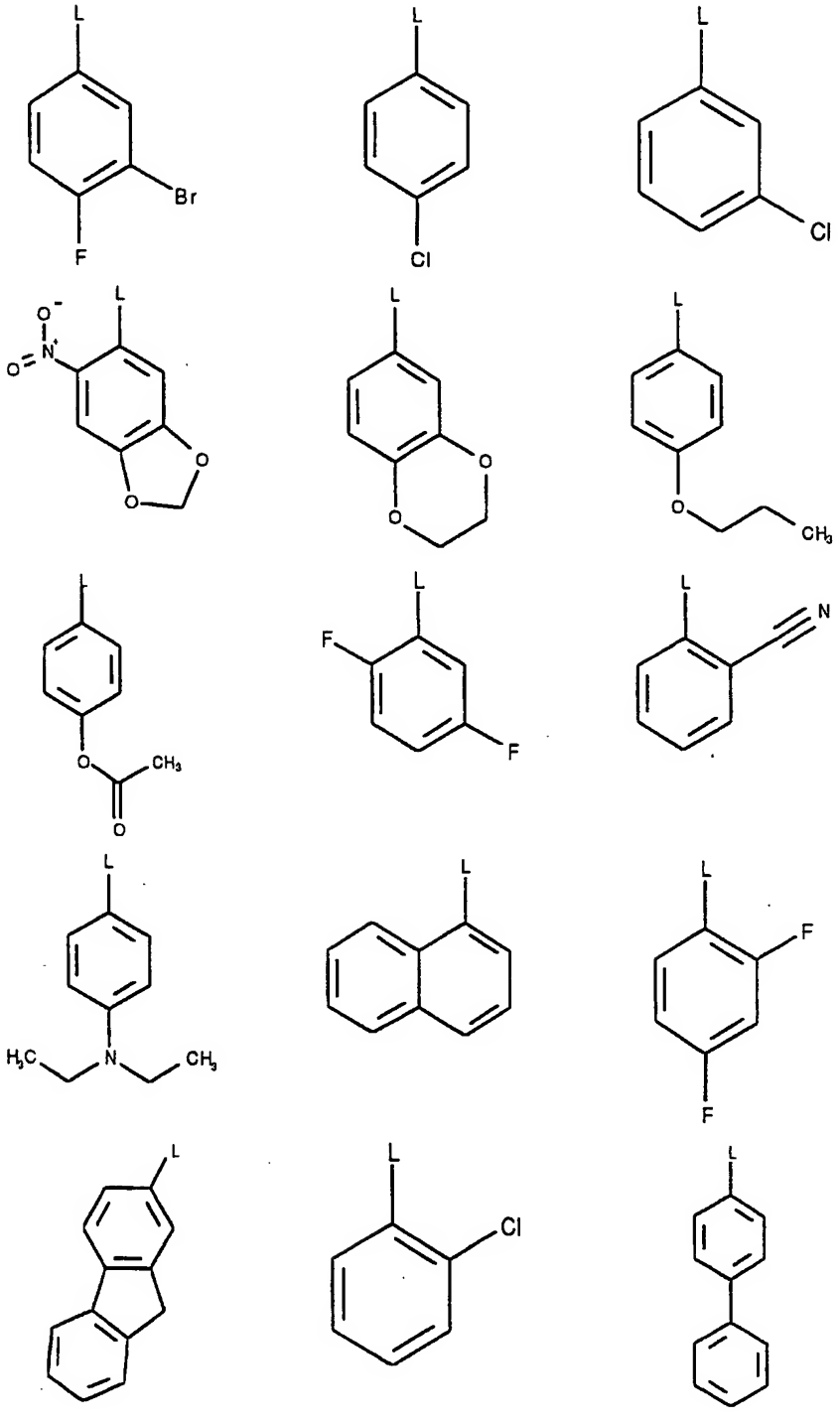
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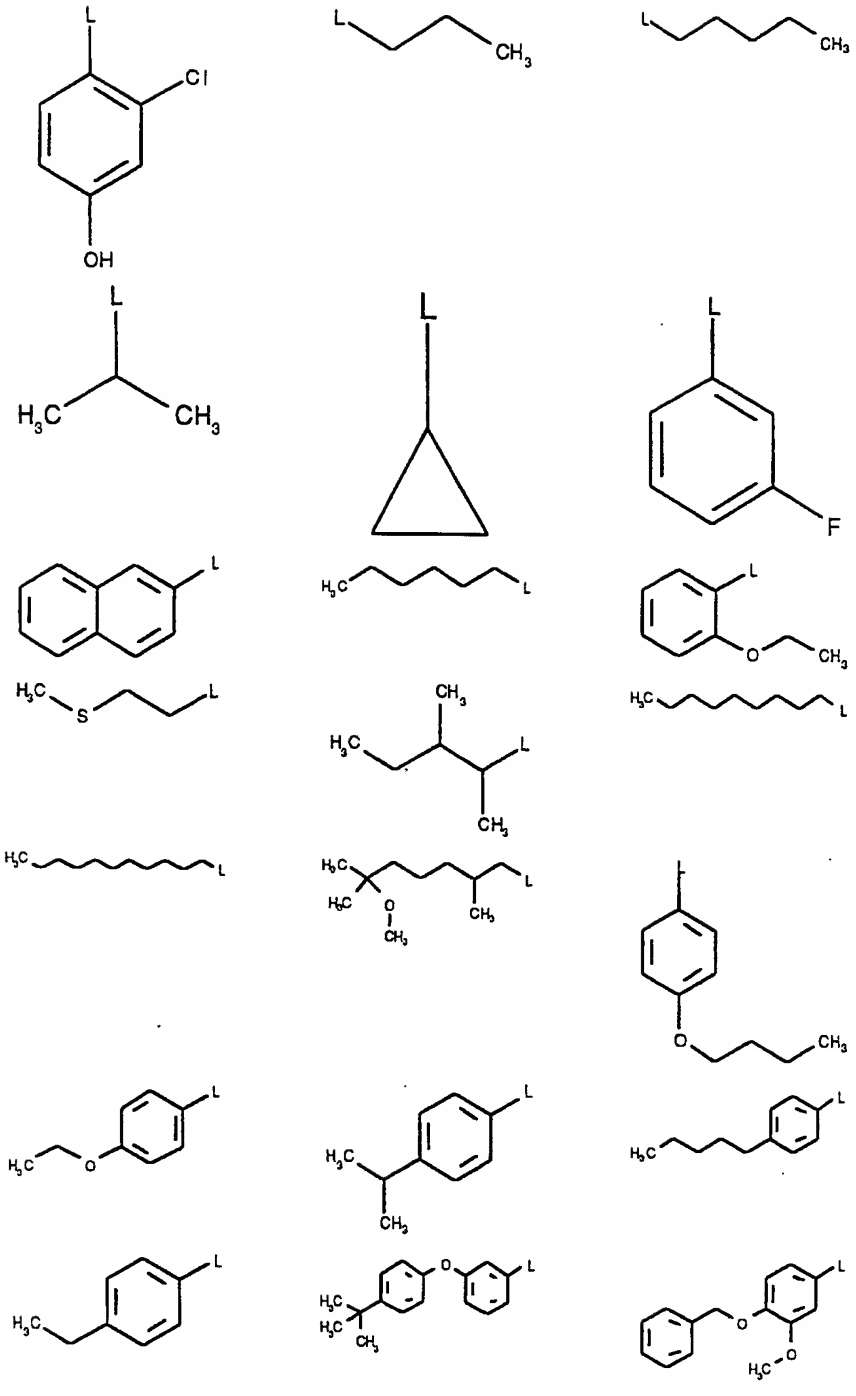
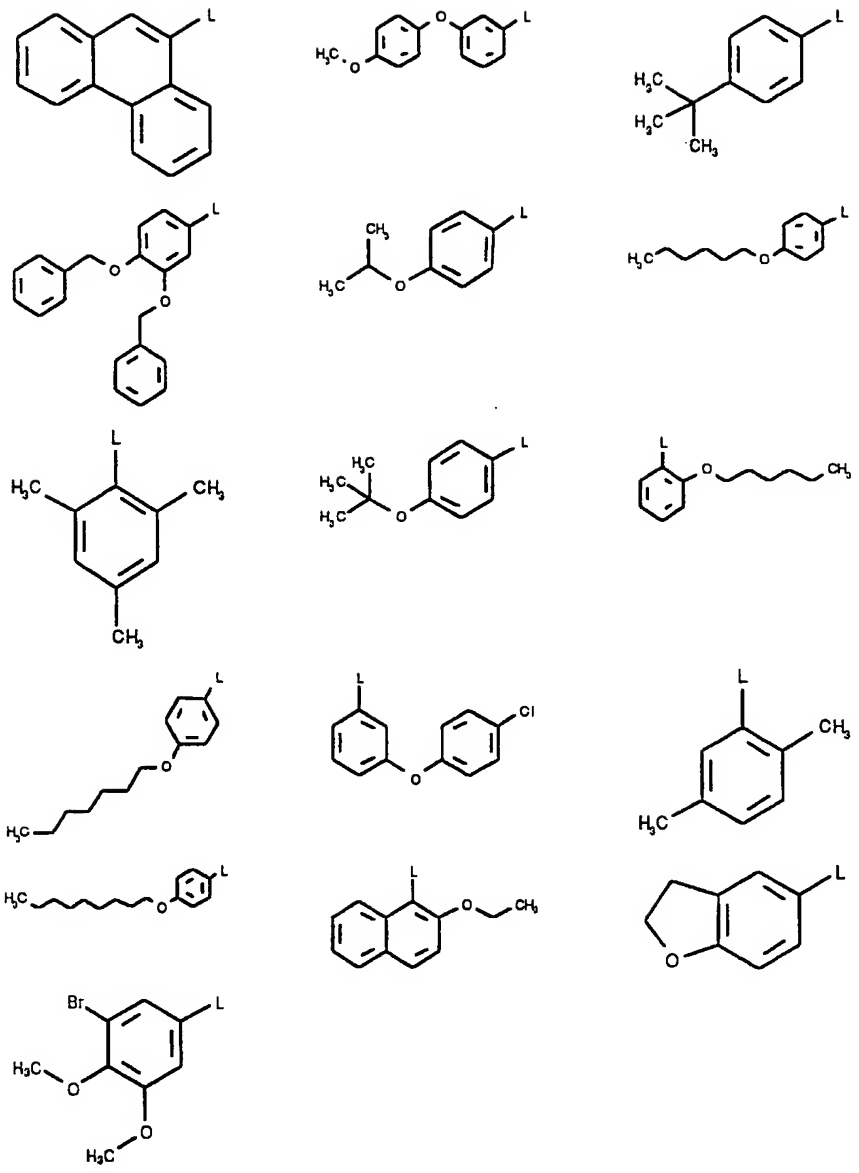




The preparation of the tetrahydroquinoline library compounds of Formula I above comprises a one-step process wherein an optionally substituted aniline, an optionally substituted aldehyde and cyclopentadiene are allowed to react in the presence of acid, typically a protic acid and/or a Lewis acid, for example, trifluoroacetic. The progress/completion of the reactions can be determined by

a number of conventional techniques including thin layer chromatography (TLC).

The reaction is carried out at ambient temperature in acetonitrile, preferably in a single reaction step. Alternatively, the reaction can be carried out as a two step process: (1) an intermediate imine forming step by reaction of equivalent amounts of an aldehyde and an optionally substituted aniline and (2) protic acid catalyzed cycloaddition of the intermediate imine with cyclopentadiene. A reaction zone charged with the reagents in the following preferred sequence, each typically in solution in acetonitrile:

1) optionally substituted aniline;
2) trifluoroacetic acid (about 0.1 to about 1 molar equivalents based on the amount of aniline reactant);
3) cyclopentadiene (about 4 molar equivalents based on the amount of aniline reactant); and
4) aldehyde (about 1 molar equivalent per amount of aniline reactant).

The reaction zone is then sealed and shaken at ambient temperature for about 12 to about 24 hours. The reaction mixture is then evaporated by vacuum to provide a library compound in each reaction zone. Preferably the product is dissolved in a mixture of acetone, methanol and methylene chloride and the resulting solution is evaporated to promote removal of residual volatiles. Samples of each library compound can be analyzed by chromatographic, or more preferably chromatographic and mass spectral techniques.

The process of the present invention utilized in preparation of a library of tetrahydroquinolines of Formula I above may be carried out in any vessel capable of holding the liquid reaction medium. In one embodiment, the process of the invention is carried out in containers adaptable to parallel array synthesis. In

particular, the tetrahydroquinoline library of this invention can be formed in a 96-well plate as illustrated in Figures 1 and 2. That apparatus provides multiple reaction zones most typically in a two-dimensional array of defined reservoirs, wherein one member of the tetrahydroquinoline library of this invention is prepared in each reservoir. Thus the diverse tetrahydroquinoline library of the present invention comprises a plurality of reservoir arrays (e.g. well plates), each reservoir or well containing a library compound of the tetrahydroquinoline library. Accordingly the library compounds are typically identified by reference to their well plate number and their X column and Y row well plate coordinates.

Following simultaneous preparation of the library member compounds in the reservoir array, the compounds can be transferred in whole or in part to other reservoir arrays (e.g. well plates), to prepare multiple copies of the library apparatus or to subject the library to additional reaction conditions. Copies of the library apparatus (daughter well plates, each comprising a 2-dimensional array of defined reservoirs with each reservoir containing a predetermined member of the library) are useful as replaceable elements in automated assay machines. The apparatus of this invention allows convenient access to a wide variety of structurally related tetrahydroquinoline compounds. One preferred reservoir array for use in making and using this invention is a multi-well titer plate, typically a 96-well microtiter plate.

Figure 1 illustrates the top surface of a well plate apparatus of the present invention. The well plate (1) is a plastic plate with 96-wells (depressions) capable of holding liquids for parallel array synthesis. Individual reaction products are prepared in each well and are labeled by the well plate coordinates. For example, the

library compound at location (2), is identified by the alpha numeric coordinate, "A6".

Figure 2 illustrates a side view of a modified well plate apparatus for use in preparation of the library of the present invention. Well plate (3) contains wells (4) with a filter (5), and a retaining frit (6), and a liquid reaction medium used in carrying out the process (7). The wells have an outlet at the bottom which is sealed by gasket (8) held in place by a top cover (9) and bottom cover (10) maintained in position by clamps (11).

Such well plates are typically prepared using standard 96-well plates. A hole is drilled in the bottom of each well in the plates and a porous frit is placed in the bottom of each well. The plate is then placed in the clamp assembly to seal the bottom of the wells.

Synthesis is initiated by adding reagents to their individual wells according to their assigned plate coordinates. The plate is then capped and tumbled to mix the reagents. Following completion of the reaction, the solvent and residual volatile reagents are evaporated with a Speed-vac. The residual products are redissolved in appropriate liquid solvent and the reaction products analyzed, for example, by thin layer chromatography, mass spectrometry and/or nuclear magnetic resonance spectrometry.

One embodiment of the present invention is an assay kit for the identification of pharmaceutical lead compounds. The assay kit comprises as essential parts, (1) a well plate apparatus (containing one of the tetrahydroquinoline compounds in each of its individual wells), and (2) biological assay materials. The biological assay materials are generally known to be predictive of success for an associated disease state. Illustrative of biological assay materials useful in the kit of this invention are those required to conduct

assays known in the art, which include, but are not intended to be limited to:

In vitro assays, such as:
Enzymatic inhibition,
Receptor-ligand binding,
Protein-Protein interaction,
Protein-DNA interaction,
and the like;

Cell based, functional assays, such as:
Transcriptional regulation,
Signal transduction/Second messenger,
Viral Infectivity,
and the like; and

Add, Incubate, & Read assays, such as:
Scintillation Proximity Assays,
Angiotensin II IPA receptor binding assay,
Endothelia converting enzyme [$^{125}$I] SPA assay,
HIV proteinase [$^{125}$I] SPA enzyme assay,
Cholesteryl ester transfer (CETP) [$^{3}$H] SPA assay,
Fluorescence Polarization Assays,
Fluorescence Correlation Spectroscopy,
Calorimetric biosensors,
$Ca_2^+$ - EGTA for Cell-based assays,
Receptor Gene Constructs for cell based assays;
Cellular reporter assays utilizing, for example, reporters such as luciferase, green fluorescent protein, Beta-lactamase, and the like
Electrical cell impedance sensor assays
and the like.

Example 1.

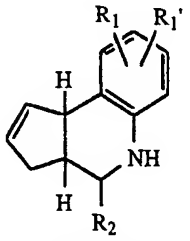
Tetrahydroquinoline Library Plates: General Procedure.

A different optionally substituted aniline reagent (100 µL of a 0.5 M solution in $CH_3CN$) was added to the wells of each row of a (several) 96-well glass titer plate (well volume of 1 mL), with care taken that all liquid was added to the bottom of the wells and with minimum splattering. Trifluoroacetic acid was then added to each well (100 µL of a 0.45 M solution in $CH_3CN$), followed by a freshly prepared solution of cyclopentadiene (125 µL of a 1.6 M solution in $CH_3CN$). A different aldehyde (100 µL of a 0.5 M solution in $CH_3CN$) was then added to the wells of each column in the plate(s). The wells were capped and the plates shaken at ambient temperature overnight.

The solvent and residual volatile reagents were then evaporated in a Speed-Vac. The residue in each well was then dissolved in a suitable of solvents, for example, a 3:4:3 mixture of acetone, methanol and methylene chloride. This process afforded plates containing about 40 µmol of a library compound per well. Prior to final drying, samples of solution were taken from each well and submitted for thin layer chromatography and/or mass spectral analysis.

I claim:

1. A library of tetrahydroquinoline compounds wherein said library contains a plurality of diverse library compounds of the formula



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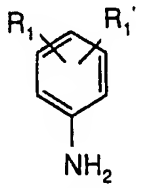
wherein $R_1$ and $R_1'$ are independently hydrogen or a non-interfering substituent derived from an optionally substituted aniline of the formula



and $R_2$ is hydrogen or an organic moiety derived from an aldehyde of the formula $R_2CHO$.

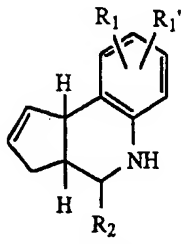
2. The library of claim 1 wherein $R_1$ and $R_1'$ are independently selected from the group consisting of hydrogen and non-interfering substituents and $R_2$ is hydrogen, alkyl, substituted alkyl, or aryl.

3. The library of claim 1 wherein the optionally substituted aniline has a molecular weight of about 93 to about 600.

4. The library of claim 1 wherein the aldehyde has a molecular weight of about 44 to about 700.

5. A compound selected from the group consisting of the library compounds of the library of claim 1.

6. A process for preparing a combinatorial library of tetrahydroquinoline compounds of the formula

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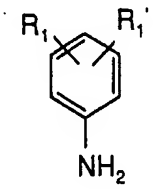
having diversity in substituent groups $R_1$, $R_1'$, and $R_2$, wherein each library compound is made in a separate reaction zone, said process comprising the step of reacting an optionally substituted aniline of the formula



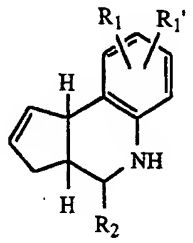

with an aldehyde of the formula $R_2CHO$ and cyclopentadiene in the presence of an acid, wherein in the above formulas $R_1$ and $R_1'$ are independently selected from the group consisting of hydrogen and non-interfering substituents and $R_2$ is hydrogen or an organic moiety.

7. An assay kit for identification of pharmaceutical lead compounds, said kit comprising biological assay materials and a well plate apparatus wherein each well in said apparatus contains a library compound of the library of claim 1.

8. The assay kit of claim 7 wherein the biological materials are selected for performing at least one assay test selected from the group consisting of *in vitro*

assays, cell based, functional assays, and add, incubate, and read assays.

9. An apparatus suitable as a replacement element in an automated assay machine as a source of individual members of a library of structurally related compounds, said apparatus comprising a 2-dimensional array of defined reservoirs, each reservoir containing a library compound of said library, wherein said structurally related compounds are of the formula (I):

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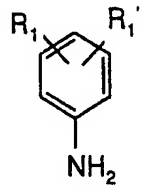
wherein $R_1$ and $R_1'$ are independently hydrogen or non-interfering substituents derived from an optionally substituted aniline of the formula




and $R_2$ is hydrogen or an organic moiety derived from an aldehyde of the formula $R_2CHO$.

10. The apparatus of claim 9 wherein the library compound in each reservoir is prepared in accordance with the process of claim 6 and wherein each reservoir provides one reaction zone.

11. The apparatus of claim 9 wherein the 2-dimensional array of defined reservoirs is a multi-well microtiter plate.

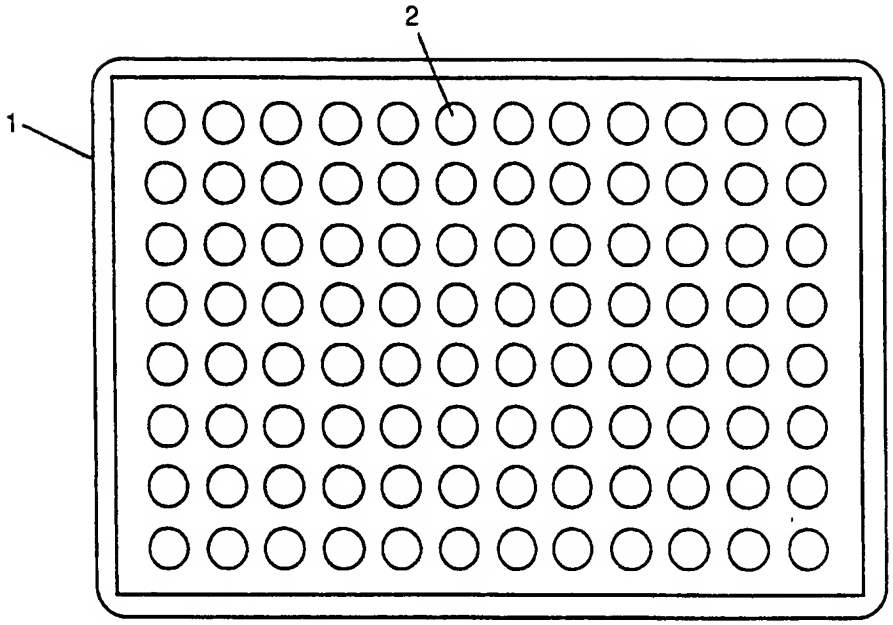
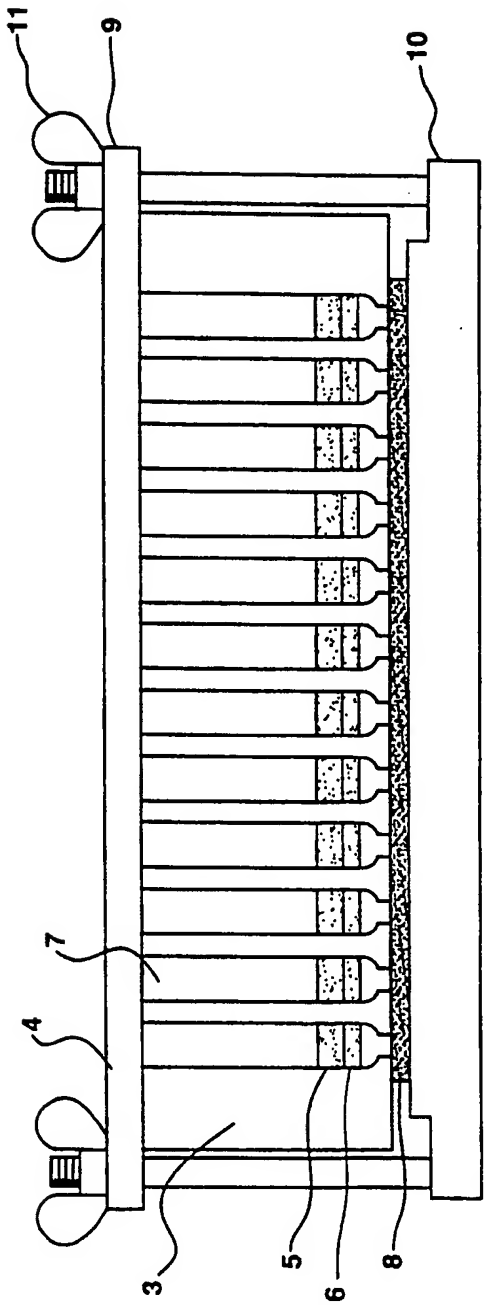



FIG. 1

FIG. 2



# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/22869

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :G01N 33/53
US CL :435/7.1; 436/501, 518

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1; 436/501, 518

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, APS
search terms: structure search, combinatorial, library, tetrahydroquinoline

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>—<br>Y | KOBAYASHI et al. Lanthanide Triflate Catalyzed Imino Diels-Alder Reactions; Convenient Syntheses of Pyridine and Quinoline Derivatives. Synthesis. September 1995. Vol. 9. pages 1195-1202, see Table 4. | 1-6<br>—<br>7-11 |
| Y | US 5,324,483 A (CODY et al.) 28 June 1994, see column 2, line 35-column 3, line 20. | 7-11 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
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| "P" | document published prior to the international filing date but later than the priority date claimed | | |

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| Date of the actual completion of the international search<br>04 MARCH 1998 | Date of mailing of the international search report<br>19 MAR 1998 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>LORA M. GREEN<br>Telephone No. (703) 308-0196 |

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